PATENT SPECIFICATION (11) 1249261

1249261

NO DRAWINGS

(21) Application No. 12449/70 (22) Filed 16 March 1970

(31) Convention Application No. P 19 13 199.8

(32) Filed 15 March 1969 in

(33) Germany (DT)

(45) Complete Specification published 13 Oct. 1971

(51) International Classification C 07 c 97/06, 97/10, 149/42; C 07 d 7/34, 13/10, 15/18, 63/12, 65/14

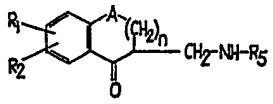
(52) Index at acceptance

C2C 173—176—185 174—271—276 175—195—288 177—198—275 179—199—278 17X—178—183 213 215 220 222 226 227 22X 22Y 246 253 254 25Y 273—280—287 29X 29Y 30Y 313 31Y 322 32Y 338 351 352 353 360 362 364 365 366 368 36Y 373 37Y 613 620 650 652 662 760 790 79Y LL LM LZ RM RN

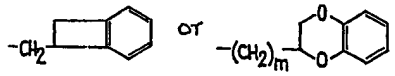
(54) MANNICH-BASES

(71) We, BEIERSDORF AKTIENGESELLSCHAFT, a German Company of 2000 Hamburg 20, Unnastrasse 48, Germany, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to novel therapeutically valuable Mannich bases of the general formula



in which R_1 and R_2 are hydrogen, hydroxyl, lower alkyl, alkoxy or acyloxy groups, n is 0, 1 or 2 and A is a methylene group or a group R_3 R_4 C< where one or both of R_3 and R_4 are alkyl groups, or n is 1 and A is oxygen or sulphur, and R_5 is an arylalkyl, aryloxyalkyl or arylthioalkyl group, in which the alkyl portion is constituted by a straight or branched chain alkyl residue containing 2 to 4 carbon atoms, optionally substituted by a hydroxyl group, and the aryl portion comprises a phenyl, naphthalene or thiophene residue optionally substituted by one or more substituents, selected from halogen atoms, hydroxyl groups, lower alkyl and alkoxy groups, or in which two neighbouring carbon atoms of the said residue are linked in a ring *via* a methylene dioxy group, or R_5 is a group of the formula



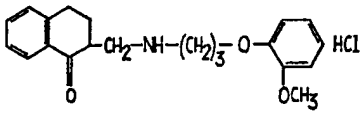
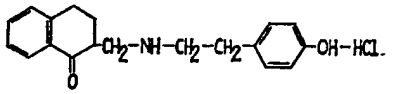
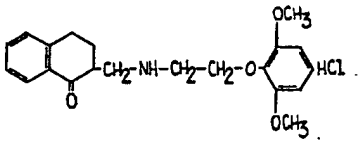
wherein m is 1 or 2, and their physiologically acceptable acid addition salts.

In the foregoing formula, R_1 and R_2 may be the same or different within the meanings given. By the term lower alkyl, lower alkoxy and lower acyloxy group, is to be understood those groups containing up to 6 and preferably 1—3 carbon atoms in the molecule.

The new compounds of the general formula given and their acid addition salts, are distinguished by a strong α-sympathicolytic action. In animal tests they are approximately equivalent in action to the known very effective α-sympathicolytic 2-(N-*p*-tolyl-N-*m*-hydroxyphenyl aminomethyl)-imidazoline (international short name: Phentolamin), though some of them are better, as is evident from the following table, in which the results of comparative tests are set out, in which three of the new com-

pounds of the invention are compared with Phentolamin (in the form of the methyl sulphonic acid salt). In these tests, which were carried out according to the method of Shipley & Tilden (Proc. Soc. Biol., N.Y., *64* (1947), page 453), dose action curves were drawn for Noradrenalin for decerebrated despinalised living rats, and the effective dose (ED_{50}) determined for noradrenalin before and after the α-blocking by means of the substance under test. The quotient of the two ED_{50} values gives an indication of the α-sympathicolytic action.

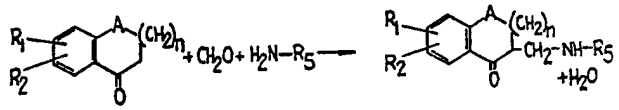
TABLE

Substance	Dose (mg/kg)	ED_{50} before α-blocking / ED_{50} after α-blocking
	5	116
	5	86
	5	64
Phentolamin (comparison)	5	95

As is evident from the table, a new class of theraputically valuable compounds has been discovered with strong α-sympathicolytic action, comparable with the known, strongly active Phentolamin.

The Mannich bases of the invention may be used in the form of their easily crystallising acid addition salts, preferably in the form of the hydrochloride, optionally mixed with suitable liquid or solid carriers of conventional type, for the manufacture of solutions for injections and especially for orally administrable pharmaceutical preparations, such as pills, dragees or tablets.

The new compounds of the invention can be made by the known Mannich reaction process by reacting a ketone with formaldehyde or a polymeric form of formaldehyde and an amine, according to the following reaction scheme:



the symbols R_1, R_2, A, n and R_3 having the meanings assigned to them above.

The manufacture of the compounds of the invention is preferably carried out in alcoholic solution by refluxing a mixture of about 1 mol of ketone, 1 mol paraformaldehyde and about 1 mol of the aminohydrochloride necessary for the reaction, for several hours. On cooling the reaction mixture, the hydrochloride of the Mannich base generally crystallises out; it can then be isolated and purified without difficulty. For more difficultly condensable amines, the reaction mixture is preferably made acid by addition of some hydrogen chloride dissolved in ether, or the reaction is carried out in a benzene-nitrobenzene mixture with the aid of a water-separator. If at the end of the reaction and cooling of the reaction mixture, no separation or crystallisation of the salt of the Mannich base takes place, then the solvent is distilled off and the residue, taken up in hydrochloric acid and shaken with a suitable solvent, e.g. ether or benzene. After making the acid aqueous solution alkaline, the Mannich base so obtained is taken up in ether or methylene chloride and, after drying the organic phase, is reacted with ethereal hydrochloric acid solution to precipitate the hydrochloride. The salts of Mannich bases are obtained in yields of about 50 to 85% of theoretical, with a relatively high degree of purity. They can be recrystallised without difficulty from suitable solvents, preferably alcohols, and obtained as analytically pure products.

The manufacturing process described for the compounds of the invention is further illustrated by reference to the following examples.

EXAMPLE 1

2(β-phenylethylaminomethyl)-6-methoxy-1,2,3,4-tetrahydro-1-keto-naphthalene hydrochloride

A mixture of 4.4 g (0.025 mole) 6-methoxy-α-tetralone, 0.75 g (0.025 mol) paraformaldehyde, 4.0 g (0.025 mol) β-phenylethylamine hydrochloride and 25 ml isopropanol were refluxed for 5 hours with stirring. The hydrochloride of the reaction product crystallised out from the cooled reaction mixture; this was sucked off and washed with ether. The product was present in an amount of 7.2 g (84% of the theoretical yield) of melting point 170—173°. Recrystallisation from isopropanol did not raise the melting point.

EXAMPLE 2

2(β-phenylethylaminomethyl)-indanone(1)-hydrochloride

Similarly to Example 1, 0.1 mol indanone-1 (13.2 g), paraformaldehyde (3.0 g) and β-phenylethylamine hydrochloride (15.8 g) were heated under reflux with stirring in 100 ml isopropanol for about 6 hours. The hydrochloride of the Mannich base crystallised out from the cooled reaction solution. It was sucked off and washed with ether 24 g (80% of the theoretical yield) of reaction product with a melting point of 188—190° was obtained. No increase in melting point took place after recrystallisation from methanol.

EXAMPLE 3

2[β(3-methoxyphenoxy)ethylaminomethyl]-1,2,3,4,-tetrahydro-1-keto-naphthalene hydrochloride

12.2 g (0.0835 mol), α-tetralone, 2.5 g (0.0835 mol) paraformaldehyde and 17 g (0.0835 mol) of β-(m-methoxy-phenoxy) ethylamine hydrochloride were refluxed for about 5 hours with stirring in 70 ml isopropanol. After cooling, the Mannich base hydrochloride precipitated, and it was sucked off and washed with ether. The product had a melting point of 122.5—124.5°. The yield was 22. g (=76% of theoretical yield). Recrystallisation from ethanol raised the melting point to 133.5—136.5°.

EXAMPLE 4

2[β-(4-chlorophenylmercapto) ethyl aminomethyl]-1,2,3,4 tetrahydro-1-keto-naphthalene hydrochloride

A mixture of 0.1 mol α-tetralone (14.6 g), paraformaldehyde, (3.0 g), β(4-chlorophenylmercapto)-ethylamine hydrochloride (22.4 g) and 100 ml isopropanol was refluxed for about 7 hours with stirring. The product crystallizing out after cooling was sucked off and washed with ether. 29 gm of hydrochloride were recovered (=76% of theoretical yield) of melting point 181.5—183.5°. Recrystallisation from methanol did not raise the melting point.

Analogously to the foregoing examples, the following new compounds can be manufactured from the corresponding ketones and amines. After each compound, the melting point (in °C.) is given. The crystallisation solvent was ethanol except where otherwise indicated.

TABLE

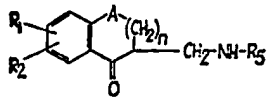
2(β - Phenylethylaminomethyl) - 1,2,3,4 - tetrahydro - 1 - keto - naphthalene hydrochloride, 161—162° (Isopropanol)
2[(α - Methyl - β - phenyl - ethyl)aminomethyl] - 1,2,3,4 - tetrahydro - 1 - keto-naphthalene-hydrochloride, 157—158° (Isopropanol)
2[(β - Methyl - β - phenyl - ethyl)aminomethyl] - 1,2,3,4 - tetrahydro - 1 - keto-naphthalene-hydrochloride, 130—131° (Isopropanol)
2[(α,α - Dimethyl - β - phenyl - ethyl)aminomethyl] - 1,2,3,4 - tetrahydro - 1 - keto-naphthalene-hydrochloride, 157—159°
2[(α - Methyl - β - hydroxy - β - phenyl - ethyl)aminomethyl] - 1,2,3,4 - tetrahydro-1-keto-naphthalene-hydrochloride, 158—159° (Isopropanol)
2[(β - Hydroxy - β - phenyl - ethyl)aminomethyl] - 1,2,3,4 - tetrahydro - 1 - keto-naphthalene-hydrochloride, 147.5—150°
2[β(4 - Hydroxyphenyl) - ethyl - aminomethyl] - 1,2,3,4 - tetrahydro - 1 - keto-naphthalene-hydrochloride, 168—170°
2[β(4 - Methoxyphenyl)ethyl - aminomethyl] - 1,2,3,4 - tetrahydro - 1 - keto-naphthalene-hydrochloride, 170—172°
2[β(3,4 - Dimethoxyphenyl)ethyl - aminomethyl] - 1,2,3,4 - tetrahydro - 1 - keto-naphthalene-hydrochloride, 156—159°
2[β(4 - Chlorophenyl)ethyl - aminomethyl] - 1,2,3,4 - tetrahydro - 1 - keto - naphthalene-hydrochloride, 177—178.5°
2[β(4 - Methylphenyl)ethyl - aminomethyl] - 1,2,3,4 - tetrahydro - 1 - keto-naphthalene-hydrochloride, 167—169°
2[(Benzocyclobutanyl(1) - methyl)aminomethyl] - 1,2,3,4 - tetrahydro - 1 - keto-naphthalene-hydrochloride, 182—185°
2[(β - Naphthyl(1) - ethyl)aminomethyl] - 1,2,3,4 - tetrahydro - 1 - keto - naphthalene hydrochloride, 175—178°
2[(β - Phenylethyl - aminomethyl) - 5,7 - dimethyl - 1,2,3,4 - tetrahydro - 1 - keto-naphthalene-hydrochloride, 194—196° (methanol)
2(β - Phenylethyl - aminomethyl) - 5 - hydroxy - 1,2,3,4 - tetrahydro - 1 - keto-naphthalene-hydrochloride, 182—186°
2(β - Phenylethyl - aminomethyl) - 5 - methoxy - 1,2,3,4 - tetrahydro - 1 - keto-naphthalene-hydrochloride, 177—179°
2(β - Phenylethyl - aminomethyl) - 6 - hydroxy - 1,2,3,4 - tetrahydro - 1 - keto-naphthalene-hydrochloride, 197—200° (water)
2(β - Phenylethyl - aminomethyl) - 6 - acetoxy - 1,2,3,4 - tetrahydro - 1 - keto-naphthalene-hydrochloride, 166—167°
2(β - Phenylethyl - aminomethyl) - 7 - methoxy - 1,2,3,4 - tetrahydro - 1 - keto-naphthalene-hydrochloride, 170—172°
2(γ - Phenyl - propyl - aminomethyl) - 1,2,3,4 - tetrahydro - 1 - keto - naphthalene-hydrochloride, 150—152°
2[γ(2 - Chlorophenyl)propyl - aminomethyl] - 1,2,3,4 - tetrahydro - 1 - keto-naphthalene-hydrochloride, 152—153°
2(δ - Phenylbutyl - aminomethyl) - 1,2,3,4 - tetrahydro - 1 - keto - naphthalene-hydrochloride, 152—155° (Isopropanol)
2(β - Phenylethyl - aminomethyl) - 4,4 - dimethyl - 1,2,3,4 - tetrahydro - 1 - keto-naphthalene-hydrochloride, 139—140°
3(β - Phenylethylaminomethyl) - chromanon(4) - hydrochloride, 174—175.5°
3[β - Phenyl - α - methyl - ethyl)aminomethyl] - chromanon(4) - hydrochloride, 162—163°
2(β - Phenoxy - ethyl - aminomethyl) - 1,2,3,4 - tetrahydro - 1 - keto - naphthalene-hydrochloride, 159—161°
2[β(2 - Methoxy - phenoxy)ethyl - aminomethyl] - 1,2,3,4 - tetrahydro - 1 - keto-naphthalene-hydrochloride, 127.5—129.5° (Isopropanol)
2[β(2 - Methoxy - phenoxy)propyl - aminomethyl] - 1,2,3,4 - tetrahydro - 1 - keto-naphthalene-hydrochloride, 146—149°
2[β(2,6 - Dimethoxy - phenoxy)ethyl - aminomethyl] - 1,2,3,4 - tetrahydro - 1 - keto-naphthalene-hydrochloride, 132.5—134.5° (Isopropanol)
2[β(4 - Methoxy - phenoxy)ethyl - aminomethyl] - 1,2,3,4 - tetrahydro - 1 - keto-naphthalene-hydrochloride, 145—147°
2[β(4 - Methyl - phenoxy)ethyl - aminomethyl] - 1,2,3,4 - tetrahydro - 1 - keto-naphthalene-hydrochloride, 155—157°
2[β(3 - Methyl - phenoxy)ethyl - aminomethyl] - 1,2,3,4 - tetrahydro - 1 - keto-naphthalene-hydrochloride, 133.5—135.5°

2[β(2 - Methyl - phenoxy)ethyl - aminomethyl] - 1,2,3,4 - tetrahydro - 1 - keto-naphthalene-hydrochloride, 162—164°
2[β(2 - Chlor - phenoxy)ethyl - aminomethyl] - 1,2,3,4 - tetrahydro - 1 - keto-naphthalene-hydrochloride, 166—168°
2[β(3 - Chlor - phenoxy)ethyl - aminomethyl] - 1,2,3,4 - tetrahydro - 1 - keto-naphthalene-hydrochloride, 161—163°
2[β(4 - Chlor - phenoxy)ethyl - aminomethyl] - 1,2,3,4 - tetrahydro - 1 - keto-naphthalene-hydrochloride, 167—169°
2[β(2,6 - Dimethyl - phenoxy)ethyl - aminomethyl] - 1,2,3,4 - tetrahydro - 1 - keto-naphthalene-hydrochloride, 138.5—139.5° (Isopropanol)
2[β(2,3 - Dimethyl - phenoxy)ethyl - aminomethyl] - 1,2,3,4 - tetrahydro - 1 - keto-naphthalene-hydrochloride, 168—170°
2[β(3,5 - Dimethyl - phenoxy)ethyl - aminomethyl] - 1,2,3,4 - tetrahydro - 1 - keto-naphthalene-hydrochloride, 151—153°
2[β(2,5 - Dimethyl - phenoxy)ethyl - aminomethyl] - 1,2,3,4 - tetrahydro - 1 - keto-naphthalene-hydrochloride, 142.5—144.5°
2[β(3,4 - Dimethyl - phenoxy)ethyl - aminomethyl] - 1,2,3,4 - tetrahydro - 1 - keto-naphthalene-hydrochloride, 175.5—177.5°
2[β(2,4 - Dichlor - phenoxy)ethyl - aminomethyl] - 1,2,3,4 - tetrahydro - 1 - keto-naphthalene-hydrochloride, 168—170°
2[β(3 - Methyl - 4 - chlor - phenoxy)ethyl - aminomethyl] - 1,2,3,4 - tetrahydro - 1-keto-naphthalene-hydrochloride, 176.5—179.5° (Methanol)
2[β(2 - Methyl - 4 - chlor - phenoxy)ethyl - aminomethyl] - 1,2,3,4 - tetrahydro - 1-keto-naphthalene-hydrochloride, 164—168°
2[β(3,5 - Dimethyl - 4 - chlor - phenoxy)ethyl - aminomethyl] - 1,2,3,4 - tetrahydro-1-keto-naphthalene-hydrochloride 176.5—179.5° (Methanol)
2[(1,4 - Benzodioxanyl - 2)methyl - aminomethyl] - 1,2,3,4 - tetrahydro - 1 - keto-naphthalene-hydrochloride, 161—163°
2[β(1,4 - Benzodioxanyl - 2)ethyl - aminomethyl] - 1,2,3,4 - tetrahydro - 1 - keto-naphthalene-hydrochloride, 173—175°
3[β(2 - Methoxy - phenoxy)ethyl - aminomethyl] - chromanon(4)hydrochloride, 145—147°
2[β(Phenylmercapto)ethyl - aminomethyl] - 1,2,3,4 - tetrahydro - 1 - keto - naphthalene-hydrochloride, 145—147°
2[β(Thienyl - 2)ethyl - aminomethyl] - 1,2,3,4 - tetrahydro - 1 - keto - naphthalene-hydrochloride, 161—164° (Methanol)
3(β - Phenylethyl - aminomethyl) - thiochromanon - hydrochloride, 169—171° 85% ethanol
2(β - Phenylethyl - aminomethyl) - 7 - hydroxy - 1,2,3,4 - tetrahydro - 1 - keto-naphthalene-hydrochloride, 163—166°
2[β(3,4 - Methylendioxyphenyl)ethyl - aminomethyl] - 1,2,3,4 - tetrahydro - 1 - keto-naphthalene-hydrochloride, 181—183°
2[β(3 - Methoxy - 4 - hydroxy - phenyl)ethyl - aminomethyl] - 1,2,3,4 - tetrahydro-1-keto-naphthalene-hydrochloride, 156—158°
2[β(2 - Hydroxy - 3 - methoxy - phenyl)ethyl - aminomethyl] - 1,2,3,4 - tetrahydro-1-keto-naphthalene-hydrochloride, 135—136.5° (Isopropanol)
3[β(2,6 - Dimethoxy - phenoxy)ethyl - aminomethyl] - chromanon(4) - hydrochloride, 131—133° (Isopropanol)
4(β - Phenyl - ethyl - aminomethyl) - 1,2 - benzocycloheptanon(3) - hydrochloride, 136—138°
3(β - Phenylmercapto - ethyl - aminomethyl) - thiochromanon(4) - hydrochloride, 148—150°
3[β(4 - Hydroxy - phenyl)ethyl - aminomethyl] - chromanon(4) - hydrochloride, 166—168°
2[β(4 - Hydroxy - phenyl) - ethyl - aminomethyl] - indanon(1) - hydrochloride, 182—185°
2(β - Phenyl - ethyl - aminomethyl) - 6(3,4,5 - trimethoxybenzoyl - oxy) - 1,2,3,4-tetrahydro-1-keto-naphthalene-hydrochloride, 180—182° Methanol
2[β(2 - Methoxy - phenoxy)ethyl - aminomethyl] - indanon(1) - hydrochloride, 124—126° (Isopropanol)
3[β - (2,6 - Dimethoxy - phenoxy)ethyl - aminomethyl] - thiochromanon(4) - hydrochloride 125—127° (Acetone)
3[β - (4 - Chlor - phenylmercapto)ethyl - aminomethyl] - thiochromanon(4) - hydrochloride, 174—175°

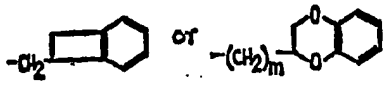
2[β(2 - Hydroxy - phenyl)ethyl - aminomethyl] - 1,2,3,4 - tetrahydro - 1 - keto-naphthalene-hydrochloride, 167—170° (Isobutanol).

WHAT WE CLAIM IS:—

1. A Mannich base of the general formula



in which R_1 and R_2 are hydrogen, hydroxyl, lower alkyl, alkoxy or acyloxy groups, n is 0, 1 or 2 and A is a methylene group or a group R_3 R_4 C< wherein one or both of R_3 and R_4 are alkyl groups or n is 1 and A is oxygen or sulphur, and R_5 is an aryl-alkyl, aryloxyalkyl or arylthioalkyl group, in which the alkyl portion is consituted by a straight or branched chain alkyl residue containing 2 to 4 carbon atoms, optionally substituted by a hydroxyl group, and the aryl portion comprises a phenyl, naphthalene or thiophene residue, optionally substituted by one or more substituents selected from halogen atoms, hydroxyl groups and lower alkyl and alkoxy groups, or in which two neighbouring carbon atoms of the said residue are linked in a ring *via* a methylene dioxy group, or R_5 is a group of the formula

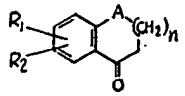


where m is 1 or 2, or a physiologically acceptable acid addition salt thereof.

2. A compound according to claim 1 as defined in any one of the foregoing specific Examples 1—4.

3. A compound according to claim 1 which is one of the compounds identified in the foregoing Table.

4. A process for the production of a compound as defined in claim 1 which comprises reacting a compound of the general formula



with formaldehyde or a polymeric form of formaldehyde and an amine of the formula $H_2N—R_5$.

5. A process according to claim 4 substantially as described with reference to any one of the foregoing specific Examples 1—4.

6. A pharmaceutical composition which comprises a compound as defined in claim 1 together with a solid or liquid diluent.

7. A pharmaceutical composition according to claim 6 in the form of an injectable solution.

8. A pharmaceutical composition according to claim 6 in the form of a tablet, pill or dragee suitable for oral administration.

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Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1971.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.